“PROGNOSTIC SIGNIFICANCE OF NUTRITION AND IMMUNITY IN HEAD AND NECK CANCER- A PROSPECTIVE OBSERVATIONAL STUDY.”

SYNOPSIS SUBMITTED

by

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For Ph.D. Degree in Oncological Sciences

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DECLARATION

I declare that the synopsis entitled **"Prognostic Significance Of Nutrition And Immunity In Head And Neck Cancer- A Prospective Observational Study"** to be submitted for the degree of PhD is my original work and it has not formed the basis for the award of any degree, diploma, association or fellowship of similar titles. The study has not been submitted to any other University or Institution for the award of any degree or diploma.

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Abbreviations

1. HNSCC- Head And Neck Squamous Cell Carcinoma
2. ESPEN- European Society For Parenteral and Enteral Nutrition
3. NCCN- National Comprehensive Cancer Network
4. SGA- Subjective Global Assessment
5. CRI - Cancer Research Institute
6. SRHU- Swami Rama Himalayan University
7. ECOG- Eastern Cooperative Oncology Group grading system
8. MUAC- Mid Upper Arm Circumference
9. BMI- Body Mass Index
10. TLC- Total Lymphocyte Count
11. DLC- Differential Lymphocyte Count
12. N/L ratio- Neutrophil to Lymphocyte Ratio
13. TNM- Tumor Node Metastasis
14. EDTA- Ehtylene-diamine-tetra-acetate
15. WHO- World Health Organisation

16. RT- Radiation Therapy

17. FNAC- Fine Needle Aspiration Cytology

18. EBRT- External Beam Radiation Therapy

19. IMRT- Intensity Modulated Radiation Therapy

20. CTRT- Concurrent Chemo- Radiation Therapy

21. NACT- Neo-adjuvant Chemotherapy

22. GY- Gray

23. PNI- Perineural Invasion

24. ENE- Extra-nodal Extension

25. TIL- Tumor Infiltrating Lymphocytes

26. PCV- Packed Cell Volume

1. Background and Objectives

According to the 2003 report of Indian Council of Medical Research, Head And Neck Squamous Cell Carcinoma (HNSCC) is very common. In India oral cancer ranks fourth common among males and fifth common among females (1), accounting for one fourth of all male and one tenth of all female cancers(4). In a comparison between cases of cancer in India and USA for the year 2002, it was found that the incidences of oral cancer in Indian males and females were 12.8 and 7.5 persons per 100000 populations, whereas it was much lower in USA - males and females (6.3 and 3.7 persons per 100000 populations), respectively (2).

In India, it has been found that most of the cancers present in locally advanced Stage (III/IV disease) (3). The treatment consists of a multimodality approach with surgery, radiation therapy and chemotherapy.

In cancer patients the incidence of malnutrition can be anywhere between 40-80% (5). The disease factors such as site of cancer and type of treatment make the nutritional management of a HNSCC patient quite complex (6). In addition they may have a long duration of poor dietary habits and life style choices like alcohol abuse, oral tobacco usage and smoking tobacco. Patients with HNSCC usually have varying degrees of dysphagia, odynophagia, loss of weight and anorexia. The structures within the treatment field and the radiation prescription effect patient's ability to eat (7).

All these disease and lifestyle factors contribute to the malnutrition.

Malnutrition may increase the risk of infection; toxicity related to treatment and finally leads to a poor quality of life and even a reduced life expectancy (8-10). ESPEN Guidelines19 defines severe nutritional risk as:

• Weight loss more than 10-15% within 6 months.

• BMI less than 18.5 kg/m2

• Subjective Global Assessment Grade C

• Serum albumin less than 30g/L

• Inability to maintain above 60% of recommended intake for more than 10 days.

According to the NCCN guidelines all patients with HNSCC need to undergo regular nutritional assessment starting at the time of diagnosis. Identification of patients with risk of nutritional problems early and timely interventions may reduce the chances of nutrition related morbidity (11). The impact of malnutrition on patient's quality of life and tolerance to treatment cannot be underestimated but prospective studies have not shown yet an improvement in the survival secondary to nutritional interventions (12).

In various studies between 50% to 75% of HNSCC patients have been estimated to be malnourished (13, 14). The SGA (Subjective Global Assessment) score can be used as an objective measure to accurately identify the malnourished from well nourished patients (15) in addition to anthropometric measures such as- weight, body mass index, mid upper arm circumference. In a study conducted in Netherlands on 1340 newly

diagnosed patients with HNSCC being treated with radiation therapy it was found that pre treatment and during treatment weight loss of more than 10 % was associated with 5 year overall survival and disease free survival to be 42% and 71% respectively as compared to 71% and 86 % in no weight loss group ($p<0.001$) (16). After adjusting for known confounding factors like tumor stage and location this association of critical weight loss was lost for 5 year overall survival but prevailed as an independent prognostic marker for disease specific survival. The patients with HNSCC in our country are different from the west with respect to nutritional status.

In 2012 an article published in Nature emphasized how there is need to understand more clearly the interactions between nutritional status and the immune system in humans that are living in different cultural and socioeconomic settings. The interrelationship of nutrient metabolism and the immune system may occur at numerous levels which range from endocrine signaling to immune cells directly sensing nutrients (17). It is seen that during malnutrition (even of moderate severity) most host defense mechanisms may be impaired. The rapidly proliferating T cells (which respond to pathogens) are especially affected, demonstrated by a decrease in their numbers (18).

HNSCC tumors are known to produce immunosuppressive mediators affecting the immune functions in the patient. An increase in number of activated T cells occurs due to the local immunological interactions between the tumor and its infiltrating leukocytes (19). Increased numbers of neutrophils, monocytes and total leukocytes and easily measured neutrophil/lymphocyte ratio was enhanced in 20 HNSCC patients as

compared to 20 healthy control patients in a Sweden study, showing a poor survival in patients with increased neutrophil/lymphocyte ratio (20). Another study comparing 146 HNSCC patients with 54 normal controls demonstrated a significantly lower absolute numbers of CD3+, CD4+ and CD+ T cells in patients than normal controls with no difference in percentage between the T cell subtypes (21).

Head and neck cancers make up approximately one-third of all cancer cases in this country in contrast to 4–5% in the developed world (3). The treatment guidelines for HNSCC eminate mainly from the West where the patient profile, etiology, dietary habits and nutritional profile are different. The ratio of tobacco related as compared to HPV related oropharyngeal cancer has come down with decrease in use of tobacco in the West. In India ever so complex socio-economic factors in addition to Government policies contribute to a greater proportion of tobacco related HNSCC. The treatment guidelines(NCCN) for HNSCC take into consideration the TNM stage of disease as well as various poor prognostic factors (perineural invasion, vascular invasion, extracapsular lymph nodal spread, level IV,V neck node metastasis etc). Nutritional status, systemic immunity markers as early prognostic factors for HNSCC still need further exploration with well planned prospective trials in Indian patients. A low cost model using nutritional assessment and systemic immunity marker as an early prognostic marker in patients being treated for HNSCC is the need of the day.

The objectives of this study are –

1. To study the nutritional profile and systemic immunity in patients with Head and Neck Squamous Cell Carcinoma (HNSCC).

2. To study the correlation between the nutritional status and systemic immunity with outcome of treatment in patients being treated for HNSCC.

3. To develop a low cost model for early prognosis using nutritional status and systemic immunity marker in patients being treated for HNSCC.

2. Hypothesis

H_0 - There is no correlation between nutritional status and systemic immunity in patients with Head and Neck Squamous Cell Carcinoma.

H_1 - there is a positive correlation between nutritional status and systemic immunity in patients with Head and Neck Squamous Cell Carcinoma.

3. Methods

Study design- Prospective Observational Cohort Study.

This study will be performed at Cancer Research Institute, Swami Rama Himalayan University, Dehradun (CRI, SRHU).

Study population- Patients starting treatment for Head and Neck Squamous Cell Carcinoma at CRI, SRHU, Dehradun.

The following inclusion and exclusion criteria will be used-

Inclusion criteria-

Patients with diagnosed and previously untreated Head and Neck Squamous Cell Carcinoma planned for treatment at this center.

Exclusion criteria-

1. Previously treated for Head and Neck Squamous Cell Carcinoma with surgery, radiotherapy or chemotherapy.

2. Metastatic disease at presentation.

3. Unwilling to participate in the study.

4. Patient with skin, nasopharynx or oesophagus carcinoma or with metastasis from primary sites other than head and neck.

5. Neck node metastasis with unknown primary.

6. Age less than 18 years.

Recruitment-

The patient once diagnosed with Head and Neck Squamous Cell Carcinoma and planned for elective (curative or palliative) treatment with single or multi-modality will

be evaluated for inclusion in this study. They will be approached and an informed consent (**annexure-1**) will be taken before enrollment in the study. Once enrolled evaluation will commence. The patients will be followed up till 6 months after completion of the planned treatment to evaluate for disease out come.

Evaluation-

The patients will be evaluated according to the study proforma (attached) at various points of time. They will be assessed for nutritional status and systemic immunity before starting treatment and at completion of planned treatment. The disease status and overall and disease specific survival will be assessed upto 6 months (at end of planned treatment, 6 weeks, 3m and 6 months) of completion of planned treatment.

The data will be collected for the following variables-

a. base line data regarding patient demographics, disease and treatment plan.

b. ECOG performance status.

c. nutritional status – weight, SGA score, MUAC, BMI, hemoglobin.

d. systemic immunity – peripheral TLC, DLC, N/L ratio.

e. treatment toxicity and complications, discontinuation and delay of treatment.

f. disease status and overall and disease specific survival at 6 months.

The primary end points of the study will be-

1. Nutritional status and immunity before and after treatment.

2. Disease status, overall survival and disease specific survival at 6 months of completion of treatment.

Two groups will be created based on the neck nodal status of the patient-

a. N- - patients with no nodal metastasis at presentation

b. N+ - patient with nodal metastasis at presentation

The data will be documented in the proforma attached, anonymised and analysed using following statistical methods.

Sampling technique- A cohort of consecutive patients diagnosed Head and Neck Squamous Cell Carcinoma starting treatment at CRI will be screened for enrollment in this study till the sample size is reached.

Sample size calculation and sample size–

Taking the correlation coefficient between nutritional status and systemic immunity as 0.5(unknown), α at 0.5, β at 90%, design effect 1.5 the sample size was calculated to be 55 in N - group and 55 in N + group. Taking the loss to follow up rate as 20 % the final sample size is 66 in each group (total of 132 patients).

Statistical Analysis-

The data will be entered in MS Excel 2010. Statistical analysis will be performed using SPSS software version 22. The one-sample Kolmogorov-Smirnov Test will be used to determine whether the data sets are different from a normal distribution. Normally distributed data will be analyzed using a Parametric test, non-normally distributed data using Non-parametric tests and the categorical data using Chi square test. The level of significance usually denoted as α will have the following criteria: the difference will be said to be significant if $p<0.05$.

To test differences between patient demographics, tumor and treatment characteristics between good and bad outcome (disease status, overall survival and disease specific survival at 6 months), chi square test will be used regarding various variables like gender, TNM stage, ECOG performance status, Nutritional status and systemic immunity markers. Survival curves will be generated using Kaplan- Meier method and log rank test will be used to examine the difference in disease status, overall and disease specific survival between various groups. A multivariate analysis will be performed, taking into consideration various confounding factors like age, gender, TNM stage, tumor location and baseline ECOG performance status. P values of <0.05 will be considered significant. A regression analysis will be used with nutritional status and marker for systemic immunity in addition to any other significant variables to develop a model for early prognostication in relation to good and poor outcome in N- and N+ disease groups.

Definitions, variables and methods-

1. Head and Neck Squamous Cell carcinoma (HNSCC) (22)-

Head and neck squamous cell carcinoma includes primary tumor arising at the subsites-

a. the oral cavity, b. the sinuses,

c. the oropharynx, d. the hypopharynx and

e. the larynx

2. Treatment for HNSCC-

Either single modality with surgery, radiation therapy or chemotherapy, or combined modality. The treatment may be with a curative intent or palliative intent.

3. Metastatic disease-

Presence of distant metastasis, regardless of the T and N stage will be taken as metastatic disease.

4. TNM staging-

The American Joint Committee on Cancer, edition 8 schema will be used for each subsite (**annexure-2**).

5. ECOG Performance status-

The performance status of the patient will be assessed using the standard Eastern Cooperative Oncology Group grading system (**annexure-3**).

6. Weight-

The weight of the patient will be measured using Salter machine (unit 9069 PK3R-2914, d=0.1kg) in standing position.

7. SGA score-

The Subjective Global Assessment of nutritional status will be performed using the standardized scale for malnutrition screening (**annexure-4**).

8. Mid Upper Arm Circumference (MUAC)-

The MUAC is the circumference of upper arm in centimeter, measured at midway between shoulder and elbow tip on left arm (for muscle mass).

Cut-off points for screening

Target Groups	MUAC (in cm)	Malnutrition
adults	17-21 cm	Moderate malnutrition
	18-21 cm with recent weight loss	Moderate malnutrition
	<17 cm	Severe malnutrition
	<18 cm with recent weight loss	Severe malnutrition

(Nutrition Module: 5. Nutritional Assessment, 5 Aug 2017, 15:10)

9. Body Mass Index (BMI)-

BMI will be calculated using the following formula- weight in kilogram divided by height in meter squared (kg/m^2) (for body fat mass).

BMI(Kg/m2) cut-offs	Nutritional status
more than 40.0	Very obese
30.0-40.0	Obese
25-29.9	Overweight

18.5-24.9	**Normal**
17-18.49	Mild chronic energy deficiency
16-16.9	Moderate chronic energy deficiency
less than 16.0	Severe chronic energy deficiency

(Nutrition Module: 5. Nutritional Assessment, 5 Aug 2017, 15:10)

10. Anemia-

Venous blood (10 ml) will be obtained using standard phlebotomy and collected in EDTA tube. LH 750 Coulter machine (Beckman Coulter) will use volume conductivity and scatter method for obtaining the haemoglobin and hematocrit value.

WHO haemoglobin levels to diagnose anemia (gm/dl) (23)

Group	No anemia	Mild	Moderate	Severe
Non pregnant female	>= 12	11- 11.9	8- 10.9	< 8
Male	>= 13	11- 12.9	8- 10.9	< 8

11. Peripheral total and differential counts-

Venous blood (10 ml) will be obtained using standard phlebotomy and collected in EDTA tube. LH 750 Coulter machine (Beckman Coulter) will use volume conductivity

and scatter method for obtaining the total peripheral white blood cell counts and the absolute differential white blood cell counts in addition to Leishman's stained peripheral blood smear method.

12. Treatment toxicity and complications-

All complications and toxicities related to treatment (surgery, radiation therapy and chemotherapy) will be looked for prospectively and documented in the case recording form.

13. Completion of planned treatment-

Completion of planned treatment will be taken as patient undergoing planned surgery and/or planned fractions of radiation therapy and/ or planned dose of chemotherapy without any delay or interruption.

14. Delay and interruption in completion of planned treatment-

Delay of >6 weeks between planned surgery and adjuvant RT, due to any cause, will be taken as delay in completion of planned treatment. Delay in completion of planned RT once started will be taken as interruption of planned treatment.

15. Discontinuation/default of planned treatment-

Unable to complete planned treatment, due to any cause, will be taken as discontinuation in completion of planned treatment – default of treatment.

16. Disease progression-

Clinical or radiological progression of the primary tumor, regional nodes or appearance of distant metastasis as assessed from end of treatment upto 6 months after completion of treatment will be taken as disease progression.

17. Disease free-

Clinical or radiological absence of disease at the primary tumor site, regional nodes and absence of distant metastasis as assessed from end of treatment upto 6 months after completion of treatment will be taken as disease free status.

18. Stable disease-

Clinical or radiological absence of progression at the primary tumor, regional nodes and absence of distant metastasis as assessed from end of treatment upto 6 months after completion of treatment will be taken as stable disease.

19. Overall / Disease specific survival-

The length of time from the date of diagnosis of cancer, that patients diagnosed with the disease are still alive. Any death due to disease will be taken for disease specific survival. This will be studied at 6 months of completion of treatment for each patient (24).

PROFORMA

Prognostic significance of Nutrition and Immunity in Head and Neck Cancer- a prospective observational study.

NAME: **AGE: yrs** **GENDER: F / M**

UHID: **PHONE NO.:**

ADDRESS: **DATE:** **SERIAL NO.:**

Base Line Data

	Primary site	Regional metastasis	Distant metastasis	TNM stage	Biopsy	FNAC	Co-morbidities	-
Diagnosis				c T N M				-
Plan of treatment	---------	Description	Date of starting	Planned dose	Planned cycles/regimen	-	Date of completion	-
Surgery	Y /N			----------	----------	-	----------	-
RT	Y /N	EBRT IMRT CTRT Pall RT		GY/#		-		-
CT	Y /N	NACT CTRT Pall CT				-		-
Final biopsy report	Size (mm)	Grade/ type	Invasion of adjacent structures	Nearest Margin (mm)	Tumor necrosis	PNI	Vascular invasion	LN/ ENE
p T N M			Y / N		Y / N	Y/N	Y / N	
TIL	Y / N	Mild /mod/ severe						

Nutritional Assessment

	Before treatment	End of treatment 1	End of treatment 2
Date			
ECOG PS			
Weight(kg)			
Height (cm)			
MUAC (cm)			
Pallor			
Bitot spots			
SGA score			

Systemic Immunity

	Before treatment		End of treatment 1		End of treatment 2	
Date						
Hb	gm/dl		gm/dl		Gm/dl	
PCV						
TLC						
	%	Absolute	%	Absolute	%	Absolute
N						
L						
E						
Mono						
Baso						
N/L ratio						

Treatment Received

	Date	Description	Dose(Gy)/ fraction	Regimen / cycles	Complications	Delay (weeks)	Interruption (days)	Additional treatment
Surgery			----------	--------				
RT		EBRT IMRT CTRT Pall RT						
CT		NACT CTRT Pall CT	----------					

Disease outcome on follow up after completion of treatment

	At treatment completion	6 wks	3 months	6 months
Date				
Primary site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
Regional site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
Metastatic site	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear	Stable Progression Clear
		Date	Cause	
Completed treatment	Y / N			
Delay in treament	Y / N			
Interruption in treatment	Y / N			
Defaulted Treatment	Y / N			
Loss to follow up	Y / N			
Death	Y / N		Cancer Unrelated	

4. Major findings and significance of the findings

In patients being treated for HNSCC there may be a positive correlation between the nutritional status, its decline during treatment and the systemic immunity status of the patient. This may lead to major consequences on treatment outcomes, treatment tolerance and finally disease outcome and survival. The correlation between patients nutritional status and systemic immunity may be different in patient with and without nodal metastasis, as patients with nodal metastasis may have a lower immunity as compared to node negative patients irrespective of their nutritional status.

The treatment guidelines used currently worldwide do not take nutritional status and systemic immunity into consideration while prognosticating a patient with newly diagnosed HNSCC. We wish to develop a low cost model for early prognostication of HNSCC patients. In a country like India with large number of patients with HNSCC and different nutritional and lifestyle habits, we hope to benefit this group of patients using this low cost model. This will also open avenues for further research in the area of tumor biology and its interrelationship with environmental factors.

References

1. Imran Ali, Waseem A. Wani, Kishwar Saleem (2011) Cancer Scenario in India with Future Perspectives. Cancer Therapy Vol 8, 56-70

2. Fenley J, Bray F, Pisani D Me (2001) World Health Organization. GLOBOCAN 2000; Cancer incidence, mortality and prevalence worldwide. Lyon France: IARC.

3. S B Shah, S Sharma, A K D'Cruz (2016) Head and neck oncology: The Indian scenario. South Asian J Cancer Jul-Sep; 5(3): 104–105.

4. C.J.K. Francis et al.(2016) Cancer Aetiology, Epidemiology, Prevention Head and Neck Cancers. Annals of Oncology 27 (suppl_9).

5. Ollenschlager G, Viell B, Thomas W et al. (1991)Tumor anorexia: causes, assessment, treatment. Recent Results Cancer Res; 121: 249-259.

6. National Institute of Clinical Excellence. Improving outcomes in head and neck cancers - The Manual 2004; London: National Institute for Clinical Excellence.

7. Kelly LE, Ward E, Van As-Brooks CJ ed. Radiation and Chemotherapy Head & Neck Cancer: Treatment, Rehabilitation and Outcomes. San Diego: Plural Publishing Inc. 2007: 57-86

8. Nitenberg, G, Raynard, B. Nutritional support of the cancer patient: issues and dilemmas. Critical Reviews of Oncology and Haematology 2000; 34: 137-168.

9. Andreyev H, Norman A, Oates J, Cunningham D. (1998) Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer 1998; 34: 503-509.

10. DeWys W, Begg C, Lavin P et al. (1980)Prognostic effect of weight loss prior to chemotherapy in cancer patients. American J Med; 69 (4): 491-497.

11. Donnelly R, Freeman L, PG Dip, RD Nutrition in Head and Neck Cancer. Journal of ent masterclass.

12. Arends J, Bodokyb G, Bozzettic F et al. ESPEN Guidelines. Enteral nutrition in non surgical oncology. Clinical Nutrition (2006); 25: 245-259.

13. Hammerlid E, Wirblad B, Sandin C et al.(1998) Malnutrition and food intake in relation to quality of life in head and neck cancer patients. Head and Neck 20(6): 540-548.

14. Ravasco P, Monterio-Grillo I, Marques P et al.(2005) Impact of nutrition on outcome: A prospective randomised controlled trial in patients with head and neck cancer undergoing radiotherapy. Head & Neck 27 (8): 659-668.

15. Isenring I, Bauer J, Capra S. (2003) The scored Patient-generated Subjective Global Assessment (PG-SGA) and its association with quality of life in ambulatory patients receiving radiotherapy. European Journal of Clinical Nutrition 57(2): 305-309.

16. J A E Langius, S Bakker, D H F Rietveld et al. (2013) Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. British Journal of Cancer 109, 1093–109.

17. Andrew L. K., Philip P. A., Nicholas W. G. (2012) Human nutrition, the gut microbiome, and immune system envisioning the future. Nature. ; 474(7351): 327–336.

18. Sandra Gredel (2011) Nutrition And Immunity In Man. 2nd edition, ILSI Europe concise monograph serie; Dietary factors which alter the immune response 9.

19. Bose A, Chakraborty T, Chakraborty K et al. (2008) Dysregulation in immune functions is reflected in tumor cell cytotoxicity by peripheral blood mononuclear cells from head and neck squamous cell carcinoma patients. Cancer Immun, 8: 10.

20. Camilla R. M., Anne M. K., Rolf U. et al. (2012) The Activation Pattern of Blood Leukocytes in Head andNeck Squamous Cell Carcinoma Is Correlated to Survival. Plos one; December:Volume 7 : Issue 12.

21. Iris K., Bridget H., Robert L. F. et al. (2004) Decreased Absolute Counts of T Lymphocyte Subsets and Their Relation to Disease in Squamous Cell Carcinoma of the Head and Neck. Clinical Cancer Research; Vol. 10, 3755–3762.

22. Seminars In Plastic Surgery/Volume 24, Number 2, 2010.

23. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity VMNIS | Vitamin and Mineral Nutrition Information System WHO/NMH/NHD/MNM/11.1, http://www.who.int/vmnis/indicators/haemoglobin.pdf.

24. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/overall-survival.

Appendices

Annexure - I **INFORMED CONSENT DOCUMENT**

सूचित सहमति प्रपत्र

Part I: <u>Subject/Patient Information document</u> Dated-

<u>भाग 1 : विषयक / रोगी का जानकारी प्रपत्र</u>

Title of the study/protocol: "PROGNOSTIC SIGNIFICANCE OF NUTRITION AND IMMUNITY IN HEAD AND NECK CANCER- A PROSPECTIVE OBSERVATIONAL STUDY."

अध्ययन / प्रोटोकॉल का शीर्षक: "सिर और एनईकेके कैंसर में पोषण और आबादी का प्रामाणिक हस्ताक्षर - एक व्यावहारिक निरीक्षण अध्ययन।"

Ethics committee approval letter no……dated……..

आचार सहिंता समिति अनुमोदन पत्रांक संख्या दिनांक

CTRIRegistration no, (if applicable)…….

CTRI पंजीकरण संख्या (यदि लागू हो तो)

Principal Investigator with qualifications: Dr. Anshika Arora(M.B.B.S) (M.S. Surgery)

मुख्य अन्वेषक योग्यता सहित डा0 अंशिका अरोड़ा (एम0बी0बी0एस0), (एम0 एस0 सर्जरी)

Name & address of institution: CRI,SRHU, Jolly Grant Dehradun

संस्था का नाम व पतः– सी0आर0आई0 एस0आर0एच0यू0, जौलीग्रान्ट, देहरादून।

Contact No: 8126923475

दूरभाष 8126923475

Subject's /Patient's Name…….

विषयक /रोगी का नाम.

Introduction: This is an observational study for patients undergoing treatment for head and neck cancer at this institute.

परिचय अध्ययन की प्रकृति व प्रकार. यह इस संस्थान में सिर और गर्दन के कैंसर के इलाज से ग्रस्त मरीजों के लिए एक अवलोकन अध्ययन है।

Purpose: To have a better understanding of nutritional status during treatment and its effect on immunity. Also to develop a low cost prognostic tool for these patients

उददेशय उपचार के दौरान पोषण की स्थिति और प्रतिरक्षा पर इसके प्रभाव की बेहतर समझ रखने के लिए। इन मरीजों के लिए कम लागत वाले प्रोनोस्टिक टूल भी विकसित करना

Methods: Patients being treated for head and neck cancer at CRI, SRHU, Dehradun will be screened for inclusion in the study. An informed consent will be taken and thereafter they will be enrolled in the study. They will be observed for nutritional status and nutritional status at various times before and after completion of treatment. The total period of observation will be upto 6 months after completion of treatment.

विधियॉ : सीआरआई, एसआरएचयू, देहरादून में सिर और गर्दन के कैंसर के लिए मरीजों का इलाज किया जाएगा अध्ययन में शामिल करने के लिए जांच की जाएगी। एक सूचित सहमति ली जाएगी और इसके बाद वे अध्ययन में नामांकित होंगे। इलाज के पूरा होने से पहले और बाद में उन्हें पोषण की स्थिति और पोषण की स्थिति के लिए कई बार देखा जाएगा। उपचार पूरा होने के 6 महीने तक अवलोकन की कुल अवधि होगी।

Risk involved: nil

जोखिम : कुछ नहीं।

Potential benefits: nil

संभावित लाभः कुछ नहीं।

Reasonable alternatives/ possible variant treatment available: nil

उचित विकल्प/उपलब्ध संभव उपचार के प्रकारः कुछ नहीं।

Subject's responsibility: nil

विषयक के दायित्व– कुछ नहीं।

Compensation: No

मुआवजा – कुछ नहीं।

Confidentiality: Yes

गोपनियता – हाँ।

Voluntary participation: Yes

स्वैच्छिक भागीदारी– हाँ।

Financial cost of participation involved: nil

वित्तीय लागत में शामिल भागीदारी : कुछ नहीं।

Contact person: Dr. Sunil Saini (Professor, Dept of General Surgery) & Ethics Committee (Member secretary),Dr. D.C. Dhasmana for further information on any query at any time in an event of a problem.

संपर्क व्यक्ति (गाइड) ऐथिक्स कमिटी (सदस्य सचिव), किसी भी समस्या या अधिक जानकारी के लिए किसी भी समय।

Patient /legal representative initials

……Date……..

रोगी /कानुनी प्रतिनिधि दिनांक

(Thank you for taking time to read this document .If you decide to take part in this study, you will be given a copy of this information document and signed consent form to keep with you)

(इस दस्तावेज को समय निकालकर पढने के लिए धन्यवाद । आप इस अध्ययन में भाग लेने का फैसला करते हैं तो जानकारी प्रपत्र की प्रतिलिपि एवं हस्ताक्षरित सहमति प्रपत्र का एक प्रति दी जाएगी ।

Principal Investigator' Name: Dr. Anshika Arora
प्रधान अन्वेषक का नाम. डा0 अंशिका अरोड़ा (एम0बी0बी0एस0), (एम0 एस0 सर्जरी)

Name of the Institute: CRI, SRHU, Jolly Grant, Dehradun
संस्थान का नाम– सी0आर0आई0 एस0आर0एच0यू0, जौलीग्रान्ट, देहरादून।

Part II: Informed consent form

सूचित सहमति प्रपत्र

Name of the study/trial: "PROGNOSTIC SIGNIFICANCE OF NUTRITION AND IMMUNITY IN HEAD AND NECK CANCER- A PROSPECTIVE OBSERVATIONAL STUDY."

अध्ययन का नाम परीक्षण– अध्ययन / प्रोटोकॉल का शीर्षक: "सिर और एनईकेके कैंसर में पोषण और आबादी का प्रामाणिक हस्ताक्षर - एक व्यावहारिक निरीक्षण अध्ययन।"

Name of the Investigator: *(Guide)* Dr. Sunil Saini, Professor Department of General Surgery

प्रधान अन्वेषक का नाम– डा0 सुनील सैनी, प्रोफेसर सर्जरी विभाग।

Study code: …….
अध्यन सहिंता
Patient Name ……..
रोगी का नाम
Date of birth…… age……..
जन्म तिथि आयु

1. I confirm that I have read and understood the patient information sheet dated…….. for the above study on ……(drugs /procedures etc)…. and had the opportunity to ask questions which were answered to my satisfaction

1. *मैं पुष्टि करता/करती हूँ कि मैंने उपरोक्त …… अध्ययन के लिए रोगी सूचना प्रपत्र दिनांक…… को भली–भांति पढ़ व समझ लिया है और इस के बारे में मुझे प्रश्न पूछने के पूर्ण अवसर मिले जिनके सन्तोषजनक उत्तर प्राप्त हुए।*

2. I have been well informed about the potential anticipated risks, discomfort and side effects associated with ….(the trial drugs/procedures etc)…. and what I will be expected to do?

2. *मुझे …… अध्ययन से जुड़े संभावित प्रत्याषित `जोखिम, परेशानी व दुषप्रभाव और इसके लिये मुझे क्या करना है के बारे में भली–भांति सूचित किया जा चुका है।*

3. I understand that my participation is voluntary and I am free to withdraw from the study at any time without giving any reason,

without affecting my future medical care or legal rights. I shall inform the principal investigator in this regard for any precaution/ medical care required to follow.

3. *मुझे ज्ञात है कि मेरी सहभागिता स्वैच्छिक है और मैं कभी भी बिना कारण बताये इस अध्ययन से भविष्य में अपने/अपनी चिकित्सा व्यवस्था या कानूनी अधिकार को किसी भी प्रकार से प्रभावित करे बिना हटा सकता/सकती हूँ । इस संबंध में मैं किसी भी सावधानी /चिकित्सा सुविधा की जरूरत पडने पर प्रधान अन्वेषक को सूचित करूंगा/करूंगी ।*

4. I understand that the principal investigator, others workers on the principal investigator's behalf and the ethics committee HIHT University will not need my permission to look at my health record both in the respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study/ trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

4. *मुझे ज्ञात है कि प्रधान अन्वेषक, प्रधान अन्वेषक की ओर से अन्य कार्यकर्ताओं और स्वामी राम हिमालयन विश्वविधालय की नैतिकता समिति को वर्तमान अध्ययन और इससे सम्बन्धित आगे किसी भी अन्वेषण के संबंध मेंमेरे स्वास्थ्य संबधी अभिलेखों को देखने के लिए मेरी सहमति की आवष्यकता नहीं होगी, चाहे मैं इस अध्ययन/परीक्षण से अलग भी क्यों न हो जाऊं । इसके लिये मै अपनी सहमती प्रदान करता/करती हूँ।*
मैं समझता हूँ कि किसी अन्य व्यक्ति/संस्था या किसी भी प्रकाषित समाग्री में मेरी पहचान का खुलासा नहीं किया जायेगा ।

5. I agree not restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose.

5. *मै इस अध्ययन से उपजित के किसी भी डेटा या परिणामों के इस्तेमाल को प्रतिबन्धित ना करने को अपनी सहमति प्रदान करता हूँ बर्ष्ते इनका प्रयोग केवल वैज्ञानिक उद्देष्यों के लिए किया जा रहा हो।*

6. I am aware that investigator will inform, whenever the situation arises, about any new finding that develop anywhere in the world, related to my treatment which may affect any decision to continue participation in the study.

6. *मुझे ज्ञात है की विष्व में कहीं भी मेरे उपचार से सम्बन्धित किसी भी नई खोज विकसित होने की स्थिति में, जो मेरे इस अध्ययन में भागीदारी जारी रखने के किसी भी निर्णय को प्रभावित कर सकता है, मुझे अन्वेषक के द्वारा सूचित किया जाएगा।*

7. I had have time to make my decision whether or not to take part in this study/trial. I agree to take part in the above study; I have received a signed and dated copy of this consent form for my records.
7. *मुझे इस अध्ययन/परीक्षण में भाग लेने या न लेने के लिये पर्याप्त समय प्रदान किया गया। मै उपरोक्त अध्ययन में भाग लेने के लिये अपनी सहमति प्रदान करता/करती हूँ। मुझे इस सहमति प्रपत्र की एक हस्ताक्षरित व दिनांकित प्रतिलिपि अपने अभिलेखों के लिये प्राप्त हो चुकी है।*

Patient/ Legally Acceptable Representative (LAR) Name	Patient's LAR's Signature	Date and Time
Investigator/ Designee Name	Investigator/ Designee's Name	Date and Time
Witness Name	Witness's Signature	Date and Time

Annexure-2 **AJCC 8 schema for TNM STAGING**

Staging for Nasopharynx Cancer

T0 No primary tumor but EBV + neck nodes

T1 Tumor confined to Nasopharynx or extends to oropharynx, nasal cavity without parapharyngeal space invasion

T2 Tumor with extension to parapharyngeal space and / or adjacent soft tissue involvement (Pterygoids,prevertebral musc)

T3 Tumor with infiltration of bony skull base, cervical vertebrae, pterygoid plates, or paranasal sinuses

T4 Tumor with intracranial extension, invasion of cranial nerves, hypophaynx, orbit, parotid, or extensive soft tissue disease lateral to lateral pterygoid muscle

N0 No metastases

N1 Unilateral nodes < 6 cms above the lower border of cricoid or uni or bilateral retropharyngeal nodes

N2 Bilateral neck nodes , < 6 cms above lower border of cricoid

N3 Unilateral or bilateral nodes > 6 cms or extension of nodes caudal to lower border of cricoids

Staging for Oropharynx Cancer (p16 -)

Tis Carcinoma in situ

T1 Tumor 2 cm or smaller in greatest dimension

T2 Tumor larger than 2 cm but not larger than 4 cm in largest dimension

T3 Tumor larger than 4 cm in dimension or extension to lingual surface of the epiglottis

T4 Moderately advanced or very advanced disease

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral node < 3 cm and Extra nodal extension (ENE) –

N2 Metastasis in a single ipsilateral node 3-6 cm and ENE – or multiple ipsilateral nodes < 6 cm and ENE

N2a Metastasis in a single ipsilateral or contralateral node 3-6 cm and ENE –

N2b Metastasis in multiple ipsilateral nodes <6cm and ENE –

N2c Metastasis in cotralateral or bilateral nodes <6 cm and ENE –

N3a Metastasis in a single node >6cm and ENE –

N3b Metastasis in a single ipsilateral, multiple ipsilateral, contraletral or bilateral nodes of any size and ENE

Staging for oropharynx (p16 +)

T categories remain the same as p16–ve tumors, except there is no Tis and T4b

N0 No regional lymph node metastasis

N1 One or more ipsilateral lymph node < 6 cms

N2 Contralateral or bilateral nodes, all < 6 cms

N3 Any lymph node /s > 6 cms.

Staging for Oral cavity cancer

T1 - Tumor ≤ 2 cms , Depth of invasion (DOI) ≤ 5 mm

T2 - Tumor > 2 cm but ≤ 4 cm, and DOI ≤ 10 mm or Tumor ≤ 2 cm, DOI > 5 mm ≤ 10 mm

T3 - Tumor > 4 cm or tumor of any size and DOI > 10 mm

T4 - T4a : Locally advanced tumor T4b : Very advanced tumor

N- same as orophaynx (p16-)

Staging of Hypopharyngeal cancer

Tis Carcinoma in situ

T1 Tumor limited to one subsite of hypopharynx and/ or ≤ 2 cms in greatest dimension

T2 Tumor invades more than one subsite of hypopharynx, or an adjacent site, or measures more than 2 cm and not larger than 4 cm without fixation of hemilarynx

T3 Tumor larger than 4 cm in largest dimension or with fixation of hemilarynx or extension to oesophagus

T4 Moderately advanced or very advanced disease

N- same as orophaynx (p16-)

Staging for laryngeal cancer

Tis Carcinoma in situ

T1 Tumor limited to one subsite with normal cord mobility

T2 Tumor invades adjacent subsite

T3 Tumor limited to larynx with cord fixation

T4 Moderately advanced or very advanced disease

N- same as orophaynx (p16-)

Annexure-3 **ECOG PERFORMANCE STATUS**

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Annexure-4 **SUBJECTIVE GLOBAL ASSESSMENT SHEET**

Adapted from: Detsky et al., 1994; Baxter Healthcare Corporation, 1993; McCann, 1996 (Ferguson, Bauer, Banks, Capra, 1996)

Assign SGA SCORE to each criteria (where A is well nourished and C is severely malnourished)

A. Weight Change in last 6 months usual weight…….kg current weight……kg

   1. A: <5% amount wt lost……..kg %wt loss…….
   2. B: 5-10%
   3. C: >10%

B. Weight change in last 2 weeks

   1. A: Increased
   2. B: Unchanged
   3. C: Decreased

C. Dietary intake overall change

   1. A: Increased
   2. B: Unchanged
   3. C: Decreased

D. Dietary Change Duration ……. weeks

   1. A: no change; adequate
   2. B: no change; inadequate
   3. C : change; decreasing

E. Type of dietary change

   1. A:intake borderline; increasing
   2. B: intake suboptimal or decreasing or full liquid diet
   3. C: intake poor and decreasing or hypocaloric liquid diet or starvation

F. Gastrointestinal symptoms persisting >2 weeks

Nausea, Vomiting, Diarrhea, Anorexia

   1. A: none; intermittent
   2. B: some daily > 2 weeks
   3. C: all daily > 2 weeks

G. Functional capacity
overall Impairment Change
Duration ..…… weeks

1. A: no dysfunction
2. B: difficulty with ambulation/ normal activities
3. C: bed ridden

H. Functional Capacity Progression

1. A: Getting better
2. B: Unchanged
3. C: Getting Worse

I. Physical findings (rated as A = normal and C=Severe)

Physical examination	A(1)	B(2)	C(3)
SUBCUTANEOUS FAT			
Under the eyes	Slightly bulging are		Hollowed look, depression, dark circles
Triceps	Large space between fingers		Very little space between fingers, or fingers touch
Biceps	Large space between fingers		Very little space between fingers, or fingers touch
MUSCLE WASTING			
Temple	Well-defined muscle/flat	Slight depression	Hollowing, depression
Clavicle	Not visible in Males; may be visible but not prominent in females	Some protrusion; may not be all the way along	Protruding/prominent bone
Shoulder	Rounded	No square look; acromion process may protrude slightly	Square look; bones prominent
Scapula/ ribs	Bones not prominent; no	Mild depressions or bone may show	Bones prominent; significant depressions

	significant depressions	slightly; not all areas	
Quadriceps	Well rounded; no depressions	Mild depression	Depression; thin
Calf	Well developed		Thin; no muscle definition
Knee	Bones not prominent		Bones prominent
Interosseous muscle between thumb and forefinger	Muscle protrudes; could be flat in females		Muscle depression
Oedema(related to malnutrition)	No sign	Mild to moderate	Severe
Ascitis (related to malnutrition)	No sign	Mild to moderate	Severe

J. Primary underlying condition affecting nutrition

1. A: Mild
2. B: Moderate
3. C: Severe

K. Primary underlying conditions affect on metabolic demand

1. A: None
2. B: Low to Moderate
3. C; High

L. Using the above ratings estimate an overall SGA Score:

1. A: Well Nourished
2. B: Moderately malnourished
3. C: Severely malnourished

Interpretation

TOTAL SCORE: